

E.S.  
PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>P018963W0/PNH</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 99/ 01019</b>	International filing date (day/month/year) <b>01/04/1999</b>	(Earliest) Priority Date (day/month/year) <b>03/04/1998</b>
Applicant <b>UNIVERSITY COLLEGE CARDIFF CONSULTANTS LIMITED</b>		
<p>This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.</p> <p>This International Search Report consists of a total of <u>3</u> sheets.</p> <p><input checked="" type="checkbox"/> It is also accompanied by a copy of each prior art document cited in this report.</p>		
<p>1. Basis of the report</p> <p>a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.</p> <p><input type="checkbox"/> the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).</p> <p>b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:</p> <p><input type="checkbox"/> contained in the international application in written form.</p> <p><input type="checkbox"/> filed together with the international application in computer readable form.</p> <p><input type="checkbox"/> furnished subsequently to this Authority in written form.</p> <p><input type="checkbox"/> furnished subsequently to this Authority in computer readable form.</p> <p><input type="checkbox"/> the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.</p> <p><input type="checkbox"/> the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished</p> <p>2. <input type="checkbox"/> Certain claims were found unsearchable (See Box I).</p> <p>3. <input type="checkbox"/> Unity of Invention is lacking (see Box II).</p> <p>4. With regard to the title,</p> <p><input checked="" type="checkbox"/> the text is approved as submitted by the applicant.</p> <p><input type="checkbox"/> the text has been established by this Authority to read as follows:  ////</p> <p>5. With regard to the abstract,</p> <p><input checked="" type="checkbox"/> the text is approved as submitted by the applicant.</p> <p><input type="checkbox"/> the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.</p> <p>6. The figure of the drawings to be published with the abstract is Figure No. <u>      </u></p> <p><input type="checkbox"/> as suggested by the applicant.</p> <p><input type="checkbox"/> because the applicant failed to suggest a figure.</p> <p><input type="checkbox"/> because this figure better characterizes the invention.</p> <p><input type="checkbox"/> None of the figures.</p>		

ATENT COOPERATION TR. TTY  
PCT  
INTERNATIONAL PRELIMINARY EXAMINATION REPORT

REC'D 19 JUL 2000  
WIPO

PCT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference  P018963WO/PNH	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No.  PCT/GB99/01019	International filing date (day/month/year)  01/04/1999	Priority date (day/month/year)  03/04/1998
International Patent Classification (IPC) or national classification and IPC  A61K9/12		
<b>Applicant</b> UNIVERSITY COLLEGE CARDIFF CONSULTANTS LIMITED		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.		
2. This REPORT consists of a total of 6 sheets, including this cover sheet.		
<input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).		
These annexes consist of a total of 1 sheets.		
3. This report contains indications relating to the following items:		
I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application		

Date of submission of the demand  02/11/1999	Date of completion of this report  17.07.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Stoltner, A  Telephone No. +49 89 2399 8408
	

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01019

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-28                   as originally filed

**Claims, No.:**

1-12,20-35           as originally filed

13-19                   as received on                   19/06/2000 with letter of                   19/06/2000

**Drawings, sheets:**

1/3-3/3                   as originally filed

2. The amendments have resulted in the cancellation of:

- the description,       pages:  
 the claims,              Nos.:  
 the drawings,           sheets:

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- the entire international application.  
 claims Nos. 34.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01019

because:

- the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
  
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
  
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. 34 (method of treatment).

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes: Claims
	No: Claims 1-35
Inventive step (IS)	Yes: Claims
	No: Claims 1-35
Industrial applicability (IA)	Yes: Claims 1--35 (except claim 34 for some contracting states within the PCT)
	No: Claims

**2. Citations and explanations**

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**s e separat sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01019

**ad section V:**

- 1). The present application concerns an aerosol composition, comprising a propellant, a first particulate material consisting of particles with a median aerodynamic diameter within the range of 0.05 to 11 micrometers and a second particulate material comprising particles having a median volume diameter within the range of 15 to 200 micrometers, as defined in the present claim 1.
- 2). The following documents have been regarded with respect to the present application:

- D1, WO-A-9 619 968, cited in the application, relates to aerosol formulations comprising a chlorofluorocarbon propellant, a first material in form of a particulate medicament and a second material consisting of a sugar (cf. abstract). In page 2, lines 10-16, the particle size of the micronised medicament has a diameter of 1-19 micrometers which is stressed to be essential for the administration to the lungs by inhalation and on page 4, lines 18-24, the particle size of the sugars (encompassing lactose) is of about 100 microns. Although no explicit reference is made to the aerodynamic diameter of the medicament particles and to the volume diameter of the sugars particles the teaching of D1 implicitly seems to fall into the ambit of the present claim 1.
- D2, International Journal of Pharmaceutics, 118(2), 1995, pp. 229-235, Bower, C. et al., studies drug aggregates consisting of lactose and salbutamol sulphate (cf. abstract) in solid micronized form. On page 231, right col., 2nd para. (Materials and methods) D2 discloses suspensions comprising micronized lactose and salbutamol sulphate with a mean volume diameter of 3,5 micron and a propellant. On page 233, right col., 3rd para., D2 refers to an aggregate diameter of about 100 microns. In view that the present application also involves the physical phenomena of flocculation (cf. page 6, first para.) this also seems to be the case in D2. Although D2 does not expressis verbis disclose a median volume diameter of lactose ranging between 15 to 200 microns, the diameter (expressed therein as Ferets diameter) indicated therein seems implicitly to cover also the diameter of the lactose particles as defined in the present claim 1.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01019

- D3, WO-A-9 524 889, discloses inhalation compositions containing microfine particles of a medicament having a particle size in the range of between 1-10 micrometers and a lactose pellet having a diameter of from about 10-1500 micrometers (see page 2, lines 15-25 and page 3, lines 14-25. As a general rule, D3 states that the medicaments to be administered by inhalation should be of a controlled particle size in the range of 1-10 micrometers in diameter (cf. page 1, lines 20-23).
- D4, WO-A-8 707 502, refers to sprayable compositions containing a lipid and a biologically active agent in micronised form, whereby in a first form, the lipid is dissolved in a propellant with said biologically active agent being dispersed within the propellant (cf. abstract, page 3, lines 6-9, lines 32-37 and page 4, lines 1-2). Although the active compound is incorporated into the composition in a micronised form of particles with a size of 1-8 microns (cf. page 4, lines 17-24), D4 is silent on an aerosol composition containing a second particulate material with a diameter of a range between 15-200 microns.
- D5, EP-A-504 112, presents an aerosol formulation comprising hydrofluoroalkanes such as tetrafluoroethane or heptafluoropropane, therapeutical agents such as salbutamol, salmeterol or fluticasone (cf. page 4, lines 23-51 and additional appropriate ingredients and pharmaceutically acceptable excipients (cf. page 5, lines 10-36). On page 6, lines 11-16, D5 proposes a particle diameter of less than 10 microns as appropriate for administration to the respiratory tract via inhalation.
- 3). From D1 and D2 an aerosol composition as depicted in claim 1 (and the subsequent claims 2-35) seems to be known. Hence the subject-matter of the present claim 1 has to be considered as anticipated by the prior art knowledge. This also applies to the hereto appending claims, referring to compositions, as well as to containers/devices for administering said composition and to the method for manufacturing said composition.
- 4). For the assessment of the present claim 34 on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known com-

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01019

pound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. This also applies to the wording of the corresponding passage(s) in the description (page 8).

**ad section VIII:**

- 1). The subject-matter of claim 11 seems inconsistent with the corresponding passage in the description (page 11, 2nd para.).

REPLACED BY  
ART 34 AMDT

13. Composition according to any one of the preceding claims wherein the propellant is selected from chlorofluorocarbons, hydrofluorocarbons and mixtures thereof.

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14. Composition according to any one of the preceding claims wherein the propellant is selected from hydrofluorocarbons and mixtures thereof.

15. Composition according to claim 14 wherein the propellant is a hydrofluoroalkane selected from the 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and mixtures thereof.

16. Composition according to any one of the preceding claims wherein the second particulate material is selected from carbohydrates including sugars, mono-, di-, tri-, oligo-, poly- saccharides, and any physiologically acceptable derivatives, salts, forms and solvates thereof, and any mixtures thereof.

17. Composition according to any one of the preceding claims wherein the and particulate material is selected from amino acids, di-, tri-, oligo-, polypeptides, proteins and any physiologically acceptable derivatives, salts, forms and solvates thereof and mixtures thereof.

18. Composition according to any one of the preceding claims wherein the first particulate material is a medicament.

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19. Composition according to claim 18 wherein the medicament is selected from salbutamol, salbutamol sulphate, terbutaline, terbutaline sulphate, ipratropium bromide or any physiologically acceptable salts or solvates thereof; beclomethasone dipropionate, budesonide, triamcinolone acetonide or any physiologically acceptable solvates thereof; corticosteroid, bronchodilator; peptides, proteins, nucleic acids or derivatives thereof; insulin, calcitonin, growth hormone, lutenising hormone releasing hormone, leuprorelin, oxytocin or any physiologically acceptable salts or solvates thereof, or any mixture thereof.

# INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/GB 99/01019

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K9/12 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 96 19968 A (GLAXO GROUP LTD ;GREEN ALEXANDER PETER (GB)) 4 July 1996 (1996-07-04) cited in the application *cf. abstract, page 2, lines 11-31, page 3, lines 11-21, page 4, lines 18-24, lines 26-35 bridging with page 5, first para. claims *</p> <p>---</p>	1-35
X	<p>BOWER, C. ET AL.: "Fractal morphology of drug aggregates in aerosol propellant suspensions" INTERNATIONAL JOURNAL OF PHARMACEUTICS, vol. 118, no. 2, 1995, pages 229-235, XP002109732 *cf. abstract, page 231, right col., 2nd para., "Materials and methods", page 233, right col., 3rd para.*</p> <p>---</p> <p>-/-</p>	1-35

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

20 July 1999

Date of mailing of the international search report

06/08/1999

Name and mailing address of the ISA

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Authorized officer

Stoltner, A

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l Application No
PCT/GB 99/01019

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 9619968	A 04-07-1996	AU 4346996 A	JP 10511376 T	EP 0799024 A	19-07-1996 08-10-1997 04-11-1998
WO 9524889	A 21-09-1995	AU 2068995 A	ZA 9502049 A	EP 0750492 A	03-10-1995 02-01-1997 21-12-1995
WO 8707502	A 17-12-1987	AT 83145 T	US 5141674 A	DE 3783039 A	15-12-1992 21-01-1993 05-04-1989 12-10-1989 23-07-1998 25-08-1992
EP 0504112	A 16-09-1992	AU 646723 B	MX 9201082 A	AU 1218892 A	03-03-1994 17-09-1992 CA 2062854 A
		FI 921060 A		JP 4327527 A	15-09-1992 17-11-1992
		MX 9201082 A			01-09-1992

PATENT COOPERATION TREATY

PCT

**NOTIFICATION OF ELECTION**  
**(PCT Rule 61.2)**

Date of mailing (day/month/year) 09 December 1999 (09.12.99)		Washington, D.C.20231 ÉTATS-UNIS D'AMÉRIQUE
in its capacity as elected Office		
International application No. PCT/GB99/01019	Applicant's or agent's file reference P018963WO/PNH	
International filing date (day/month/year) 01 April 1999 (01.04.99)	Priority date (day/month/year) 03 April 1998 (03.04.98)	
Applicant DICKINSON, Paul, Alfred et al		

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

02 November 1999 (02.11.99)

in a notice effecting later election filed with the International Bureau on:

2. The election  was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit set by Rule 32.2(b).

<p>The International Bureau of WIPO            34, chemin des Colombelettes            1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer</p> <p>Juan Cruz</p> <p>Telephone No.: (41-22) 338.83.38</p>
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